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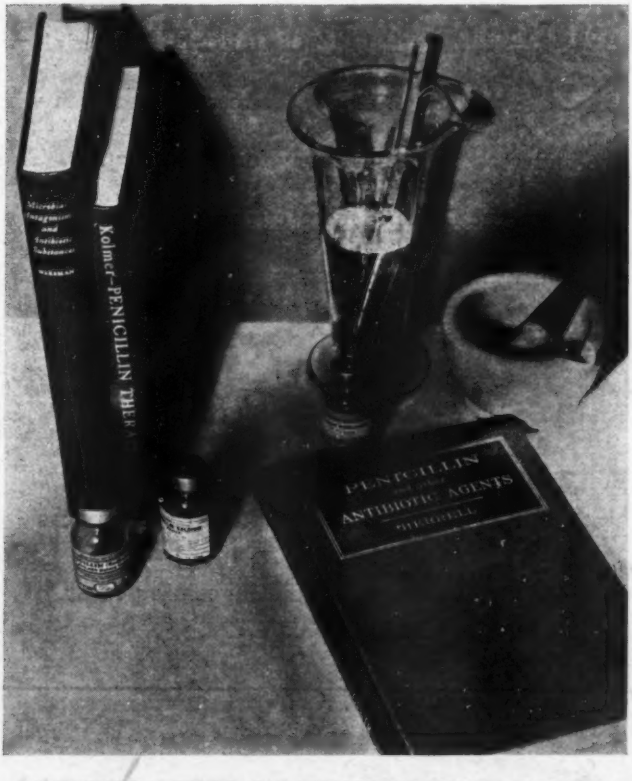

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(See our review on microbiotics in this issue)

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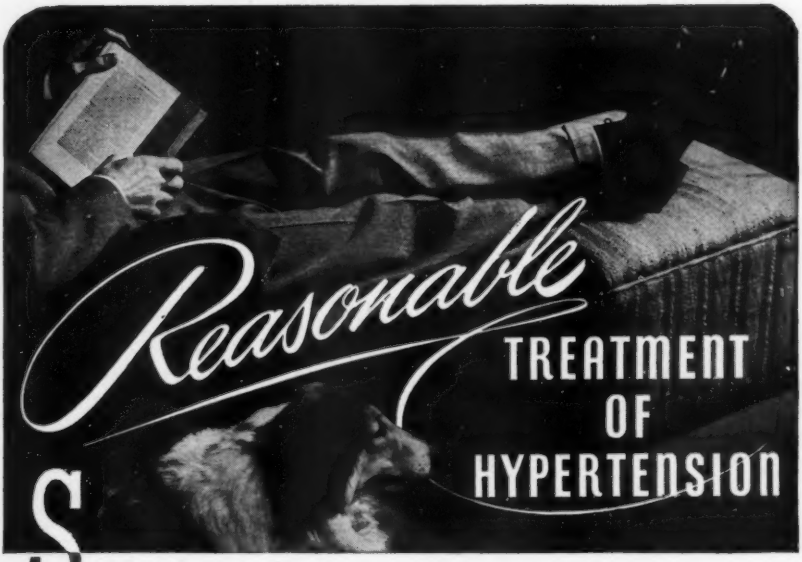

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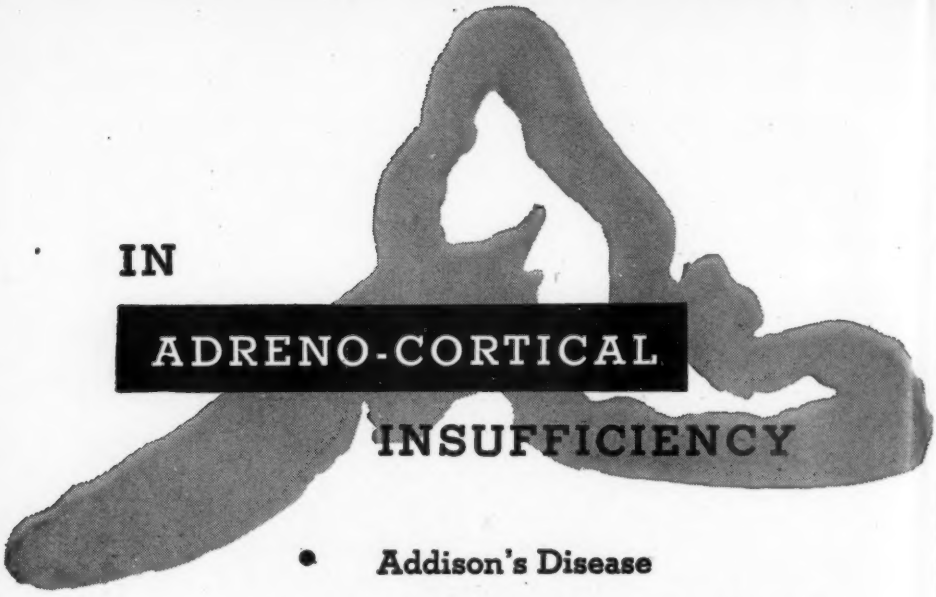

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E D I T O R I A L S

PENICILLIN—ON PRESCRIPTION ONLY?

LEGISLATION has been proposed in several states, and passed in at least one, restricting the sale of penicillin and preparations containing it to the filling of physicians' prescriptions. Such legislation is undoubtedly a reflection of medical pressure on state legislatures using the argument that the wide publicity given to penicillin will encourage many to use it for purposes of self-medication and by so doing a number of evils may arise. The laity might conceivably try to use it for diseases not amenable to penicillin therapy and, even in those wherein penicillin is a specific, inadequate or improper dosage and control might result in failures or incomplete cures. The false sense of security enjoyed by a person on penicillin therapy, particularly in venereal disease, is also advanced as a further argument against its over the counter sale.

We admit the validity of all these points submitted in favor of legislative control of penicillin sales but here indeed is a novel situation and one which deserves much more careful thought than has been given to it in some quarters. By no stretch of the imagination can penicillin be conceived as a dangerous drug. It is self-medication that is the real problem. Are we prepared to legislate this out of existence once and for all? Is it not possible to construct similar arguments for all medication taken without a physician's diagnosis and advice? We are quite sure that there are many instances wherein simple headache remedies and laxatives give to their users a false sense of security and cause the individual to delay proper medical attention, sometimes with serious results. Shall we erect similar legislation to prevent this and if we do are there enough physicians, or will there ever be, to care adequately for all those millions who now treat themselves for a variety of ailments? Will it ever be economically feasible for every person to see a physician each time he or she feels indisposed even under that reputedly Utopian plan of socialized medicine? These are questions that need to be answered and a uniform plan adopted after a careful study has been made. As it is now,

a person can buy over the counter inefficient drugs for self-medication but he is to be denied those which are not only efficient but safe. This is indeed an anomalous situation. We must not let our enthusiasm for penicillin lead us to the conclusion that here is the last word in effective medication. There is no reason to believe that no other great discoveries will be made of a similar nature. We may even some day achieve the perfect chemotherapeutic agent and infection will be conquered forever!

It may be that legislation governing the sale of penicillin is needed but so far no case has been developed for it that cannot be used for other substances. It is unfortunate if American pharmacists cannot be relied upon to exercise their professional discernment to see to it that penicillin is sold only on a proper basis. If we must have legislative control immediately placed upon us in instances such as this either we suffer from serious shortcomings or we are being subjected to misguided judgment on the part of the medical profession. There is no group less hampered by legal restrictions than the medical profession; surely they should not be so ready and willing to restrict pharmacists by proposing and supporting such on the spot legislation. We at least deserve an opportunity to prove our responsibility and our interest in public welfare.

L. F. Tice.

CERTIFIED DYES IN MEDICINAL PRODUCTS

THE use of colors in foods and medicines, either to improve or disguise the appearance of these products, has been a practice which has come down from the dawn of history. Before the introduction of synthetic compounds, the coloring matter used was of natural origin, including vegetable, mineral or animal substances.

Synthetic coal-tar dyes have been known since the middle of the last century. Their use in foods in the United States was first legalized in 1886, when such coloring matter was employed as a legitimate constituent of butter, and 10 years later, legal authorization was given for its use in cheese. During the early part of the 20th century, prior to the Food and Drugs Act of 1906, there were many Food Inspection Decisions which dealt with foods colored with intent to de-

ceive or to make the product appear as of a better quality, or of coloring matter present which was injurious to health.

In 1899, the National Confectioners Association issued a list of coal-tar dyes which were unfit for coloring food products. After the passage of the Food and Drugs Act in 1906 (effective date on January 1, 1907), various decisions on dyes were issued. Coal-tar dyes were approved in a voluntary system of certification by the Department, beginning April 1, 1908 and a list of seven colors was made available. Rules subsequently laid down as found in the Bureau of Chemistry Bulletin, No. 147, entitled "Coal-tar Colors Used in Food Products," were employed as the guide for selecting suitable colors.

The voluntary and nonremunerative system of certification of colors under the Food and Drugs Act of 1906 was changed in the Food, Drugs and Cosmetic Act of 1938 (effective date June 25, 1939). At present the use of an uncertified color in any food, drug or cosmetic shipped into interstate commerce is illegal. The certification of dyes is compulsory and is on a fee basis. There has been a marked increase in the number of certified dyes. Approximately 115 colors for drugs and cosmetics have been certified to date. The procedure for certification is described in the F. D. A. pamphlet on Coal-Tar Regulations issued in September, 1940.

It appears that the coal-tar colors which have been certified and are used in practice today, are mainly employed, inasmuch as they have proved to possess most of the following characteristics: are stable compounds, possess a standard coloring power, are free of interfering or objectionable taste and odor, are not toxic and are safe under all conditions as commonly used, do not sensitize, are capable of being assayed, and do not contain any contaminants (especially chemical and biological).

The above are effective control measures employed in the present system of certification of coal-tar products. The writer, however, wishes to point out that the possibility of an incompatibility of the coal-tar dye with the active ingredient in a medicinal product is rarely considered. This, of course, is the responsibility of the manufacturer. He, as perhaps most of us, has thought of these coal-tar dyes as comparatively inert compounds in the concentrations in which they are employed.

Recently two products of entirely different chemical composition, possessing antiseptic properties, and colored with different coal-

tar dyes were tested. When saturated aqueous solutions were prepared and examined, they were found to be ineffective as antiseptics. When solutions were prepared using these identical mixtures but in which the coal-tar dye was not present, the in vitro tests revealed findings that they possessed antiseptic properties. Additional chemical and other studies revealed incompatibilities accounting for the results obtained.

Today there is being marketed an array of preparations which are artificially colored and in which the active ingredients are present in minute quantities. The latter may be amounts which can be inactivated chemically and pharmacologically, in part or in whole by supposedly inert dyes, present also in small amounts. In view of the writer's recent experience with the two instances cited above, the industry's attention is being directed to good and safe manufacturing practice, and for its own protection to proceed to evaluate the permitted certified coal-tar dyes when used with the large array of therapeutic agents, as they are employed so frequently today. We must be assured that the mixtures are actually not incompatible and that the active ingredients in the marketed preparations have not been inactivated in whole or in part by the addition of a certified coal-tar dye.

LOUIS GERSHENFELD.

MICROBIOTICS, THEIR INDICATIONS AND USE

A Current Review

By Madeline O. Holland, D. Sc.*

A GREAT deal has been said and published about the microbiotic drugs which present one of the most striking developments in the history of the health sciences. Penicillin, of course, is the best known of these drugs, but there are others which show promising therapeutic value.

Nomenclature

The nomenclature of these various compounds has led to controversy. Chemotherapeutic compounds are substances capable of specifically injuring or destroying the living agents of disease *in vivo* without marked or serious toxic effects on the host (1). Included among these living agents are the pathogenic bacteria, spirochetes, rickettsiæ, filterable viruses, yeasts, molds and animal parasites such as protozoa and helminths.

There are innumerable substances of biologic and nonbiologic origin as well as synthetic origin which exhibit antimicrobial activity *in vitro*. Only a certain few possess this property in conjunction with a low toxicity *in vivo* to give them value as chemotherapeutic agents in the prevention and treatment of infectious diseases.

From a technical viewpoint the term microbiotics is a misnomer, when applied to the group of chemotherapeutic agents, derived directly from microorganisms. The medical dictionaries define microbiotics as short-lived or microbic.

Another term applied to these substances is "antibiotic." Since the term "biotic" refers to life or living matter, the prefix "anti" would indicate the destruction of life or living matter. In this sense all substances capable of destroying the living agents of disease *in vitro* or *in vivo* are antibiotics regardless of whether or not they are of biologic or nonbiologic origin or synthetically produced (1). In the last few years the term antibiotics has been used to designate substances produced by or derived from living cells destructive for other

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living cells. However, whatever the term, these substances do provide to the medical profession a new group of efficacious drugs for the eradication of disease. To the pharmacist they present problems in dispensing.

History

The history of penicillin and similar substances is so well known that it is not presented here.

Production

The production of penicillin and similar substances involves complex processes which are influenced by many variable factors. The yield of active substance may be materially reduced by even slight deviations from the normal procedure.

Cultures of *Penicillium notatum* from different sources may produce varying quantities of penicillin. The medium employed, its reaction, the method of cultivation, and temperature likewise influence the productivity. Aseptic precautions are necessary since certain bacteria and other organisms destroy penicillin.

The three methods generally employed for the production of penicillin are the surface culture, submerged culture, and bran culture methods (2, 3, 4). The penicillin employed in the early studies was produced mainly by the surface culture method. This involves the growing of the mold on the surface of the culture medium. At the proper time the mycelium is removed by filtration or centrifugation and the penicillin extracted from the clear filtrate by the use of selective solvents.

The submerged culture method is employed for large-scale production. In this case the mold grows beneath the surface of the medium which is both aerated and agitated. The bran method consists of growing certain strains of *Penicillium notatum* on moist bran which has been spread on trays or processed in a rotary drum.

Assay

Mention has been made of the many factors which influence the production of penicillin. For this reason it was necessary to develop methods of assay both for use as a means of control during the manufacturing process and also to study the relation of dosage and route

of administration to its therapeutic effectiveness. Following administration, it is frequently desirable to determine the blood level of penicillin at various intervals.

Thus far no chemical methods have been developed. All the present methods are microbiological and in general are based upon the degree of bacteriostatic or bactericidal activity of penicillin *in vitro* for penicillin sensitive microorganisms.

The Oxford Unit

A test for potency was ingeniously worked out by Heatley, under Florey's direction (5). Fleming's original serial dilution method, similar to that employed in usual bacteriologic procedures, was empiric and unsuited for exacting work. A modification was developed, using porcelain cups set on agar plates. Heatley defined the "unit" of penicillin antibacterial activity for the cup method as that amount of penicillin which when dissolved in 1 cc. of water gives a zone of inhibition 24 mm. in diameter, or the amount by serial dilution which when dissolved in 50 cc. of broth completely inhibits the growth of a test strain of *S. aureus*.

The "unit" of penicillin was accepted by most workers and was named in honor of Florey. However, the latter modestly disclaimed the tribute and proposed instead the now generally accepted "Oxford Unit," after its place of discovery. This term is still in use in this country, but because its measure is so small, about 0.6 microgram of penicillin, and because so many are represented in usual therapeutic procedures and industrial production, the British have invented the term "mega-unit" to indicate one million Oxford units.

The U. S. Food and Drug Administration has set up a master standard of pure crystalline penicillin sodium with a potency of 1666 units per mg. This figure was obtained as a result of numerous assays conducted by government workers and the leading penicillin manufacturers. A "reference standard," sent monthly to each manufacturer to check the potency of penicillin produced, is checked monthly against this crystalline standard by the F. D. A. In the future the dosage accordingly will be measured in milligrams on the basis of 1666 units per milligram.

The International Conference on Penicillin last October adopted an International Unit of Penicillin which was defined as the specific

penicillin activity contained in 0.6 microgram of the International Penicillin Working Standard. The International Penicillin Working Standard consists of 2.7 micrograms of calcium penicillin accepted as containing 1 International Unit of Penicillin. Manufacturers are not permitted to establish in the same manner this unitage of their own penicillin. If the standard is not available, the secondary penicillin standards accurately standardized indirectly against the authentic Oxford standard must be used.

Oxford Cup Method

The Oxford Cup Method (1, 2, 4), also known as the cylinder plate method, is commonly employed for the commercial standardization of penicillin. It is also adapted for the detection and assaying of penicillin in the serum or plasma (not whole blood), spinal fluid, exudates and other body fluids of patients under penicillin therapy (1). Under proper technical conditions it possesses an accuracy near ± 10 per cent. In principle it depends upon the diffusion of penicillin from material placed in cups in agar plates seeded with the test microorganism based upon the original hole or agar cup and gutter or impregnated strip methods of Fleming. The diffusion of the penicillin into the seeded agar produces a clear zone of inhibition of growth of the test microorganism around the cup, the diameter of which varies with the amount of penicillin in the material being assayed. The method is particularly useful when a number of assays are to be made at the same time. It is also of great value whenever exudates or contaminated fluids are being assayed since the sterility of specimens is not essential.

The procedure is carried out as follows (2): Ordinary nutrient agar plates are seeded with the test organism (*Staphylococcus aureus*) by allowing a broth culture of the organism to flow over the surface of the agar and draining off the excess broth. The plates are then dried for an hour in the incubator at 37° C. in a special rack which supports the lid of the Petri dish half an inch above the lower part. When dry the seeded plates are removed from the incubator and can be kept in the refrigerator for one or two days. Cylinders made from short lengths of glass tubing, of the proper dimensions, are placed on the agar. The lower edge of the cylinder is carefully ground level and has an internal bevel so that the thin edge tends to sink into

the agar and make a water- and bacteria-tight seal. Vitreous porcelain cylinders of the same size and shape, colored at the non-beveled end to facilitate their orientation, have also proved satisfactory. The cylinders are filled with the fluid to be tested, and the plates, resting on a block of wood, are incubated for 12-16 hours at 37° C. (If placed directly on the warm incubator shelves moisture may condense on the lids of the Petri dishes and drop on the agar, thus obscuring the results). By the end of incubation most of the fluid in the cylinders has disappeared and each cylinder is surrounded by a circular zone where no bacterial growth has occurred. The diameter of the zone depends on the concentration of the penicillin.

A standard penicillin of known unitage is tested at the same time and the values of the unknowns calculated from a standard curve. Various modifications of this technic have been recommended.

The serial dilution method is based upon the approximate determination of the highest dilutions of materials being tested which prove bacteriostatic or bactericidal for the test microorganism. In this case too, a standard penicillin should be run simultaneously. There are many variations of this method as well.

Other methods are the Fleming Slide Cell Method, the Heilman Tissue Culture Method, and the turbidimetric method (1, 2, 4).

Properties

Penicillin has been obtained as the free acid and as the barium, sodium, potassium, ammonium, calcium, silver and strontium salt. The sodium salt carries 20 to 40 per cent penicillin and it is the least toxic. It was the first salt commercially available. On April 25 the calcium salt was released.

The sodium salt is a brownish-yellow to yellow amorphous powder with a slight odor. The color varies with the method of purification. It is highly hygroscopic, absorbing moisture from the air which in turn causes a loss of potency. In the dry state all of the salts are sensitive to light. Solutions of sodium penicillin are not influenced by passage through Seitz filters (1).

The calcium salt has a number of physical characteristics which differentiate this compound from the more familiar sodium salt. It is a fine orange-brown powder. Most authorities agree that when employed parenterally in solution there is little if any clinical differ-

ence between the two substances. However, the U. S. Naval medical group, which has been receiving the greater portion of calcium salt in recent months, believes that it is preferable for a number of minor features, such as stability in pharmaceutical products. The sodium salt has proven to be of no value in suspension in oil and beeswax for intramuscular injection. In other pharmaceutical products, such as ointments, lozenges, etc., the sodium salt apparently rapidly loses its potency and therapeutic value. The calcium salt is believed to be more stable and presents a more elegant and enduring product when such extemporaneous preparations are dispensed (6).

The structural formula of penicillin is still indefinite. Various tentative condensed formulas have been suggested.

It has been reported that the type of penicillin produced depends upon the method of culturing it. Penicillin produced by the surface culture methods is known as penicillin F or penicillin I (British) and that produced in submerged culture is identified as penicillin G or II. Penicillin X (penicillin III or allopenicillin) is the term used to designate that produced by the superficial culture but extracted with chloroform. There is evidence that each fraction possesses specific therapeutic activity. The G fraction is less active against gonococci than is the crude penicillin, whereas the X fraction is more active than either.

Fractional assaying has not been made practical so that the quantity of each fraction present or the method of production is not stated on the label. The proportion of each fraction present is not consistent and may vary in each batch from the same tank or same parent mold. For this reason it is possible to explain the success or failure of penicillin in similar conditions as well as the variations in British and American products and also may be the reason for the possible inefficiency of the single-dose therapy.

Penicillin, in the form of the acid or its salts, is stable towards atmospheric oxygen but is easily oxidized by potassium permanganate and hydrogen peroxide; consequently, these agents should not be used when solutions of penicillin are employed by topical application in the treatment of wounds or other local infections. It is less sensitive to reducing agents but is not only unstable toward dilute acids, alkalis, primary alcohols and various heavy metal ions, especially Cu, Pb, Zn and Cd, but also to moist organic bases such as aniline, methyl aniline and dimethyl aniline. In aqueous solutions it is most stable

at pH 5-7 (optimum 6); at higher or lower pH, penicillin loses its antibacterial activity, the rate of inactivation depending on temperature and pH. It does not reduce Fehling's solution, but the blue color changes to green from the formation of complexes. The barium salt is strongly dextro-rotatory while the strontium salt is optically inactive. No catalytic hydrogenation takes place under atmospheric pressure with various catalysts (1).

Solubility

Free penicillin is soluble in water (to the extent of 5 mg. or about 100,000 units per cc.), isotonic saline solution, solutions of glucose, exudates and other body fluids. Free penicillin is also freely soluble in *absolute* alcohol, acetone, ethyl acetate, amyl acetate, cyclohexanone and dioxan. It is less soluble in benzene, chloroform and carbon tetrachloride, partially soluble in ether, but insoluble in alkaline solutions (1).

Stability

Penicillin in the dry form and in solution is relatively stable at low temperatures but as the temperature is increased its instability also increases. For this reason the manufacturers have advised that it be stored at 10° C. or below. At such temperatures the dry powder maintains its potency for approximately one year and the solution for several days. Penicillin solution has been found to maintain sufficient potency when stored at room temperature for 8 days for intramuscular or intravenous administration. Saline solutions (with 500 to 1000 units per cc.) for local instillation may retain sufficient potency for 3 weeks, particularly if stored in the refrigerator. Certain ointments with 500 to 1000 units per gram have been found to maintain potency for 1 month at room temperature and for 6 months in the refrigerator. Army investigation (19) reported that solutions and ointments at refrigerator temperatures showed no significant loss at the end of 60 days, but at the end of a month at room and incubator temperatures there was complete loss of activity.

A number of widely distributed bacteria such as *B. cereus, B. megatherium, B. anthracis, Esch. coli, Aerob. aerogenes, paracolon bacilli, Shig. paradysenteriæ, B. fecalis alcaligenes* and some strains of *Ps. pyocyaneus,* have been found to produce penicillinase, an enzyme which is capable of inactivating or destroying penicillin (1). The

gram-negative bacilli of the intestinal tract in particular are likely to produce it, which provides one reason for the low efficiency when given by oral and rectal administration.

Penicillin is lost rapidly even when parenterally administered. It is possible that such loss may be due to its being carried by the blood to the intestinal tract where it is inactivated or destroyed by penicillinase and excreted. Penicillinase-producing organisms may be present in sinuses, wounds and other cavities and thus inhibit the penicillin when locally applied. The organisms which generally do not produce penicillinase include the following: *Staphylococcus aureus* (most strains), *streptococci, pneumococci, meningococci, gonococci, N. catarrhalis, B. subtilis,* the Clostridia, *C. diphtheriæ, List. monomytogenes, E. typhosa,* the Salmonella, *Proteus vulgaris, Br. melitensis, H. influenzæ, H. parapertussis* and some strains of *Ps. pyocyanea.* Yeasts and fungi produce very small quantities or not at all. Takadiastase and clarase also inactivate penicillin as do certain bacterial extracts and filtrates, and cysteine. Blood, serum, pus, tissue autolysates or peptones, bacterial growth factors, amino acids, carbohydrates, phospholipids and purines do not inactivate it.

The cationic detergents such as phemerol, ceepryn and zephiran and gramicidin which behaves similarly to a detergent do not inactivate penicillin.

The mechanism by which penicillin inhibits or destroys bacteria is unknown. It is believed to be an effect upon the microorganisms themselves rather than a stimulation of the defensive powers of the host. The growth apparently is not affected but possibly some step in cellular division which prevents multiplication. Small numbers of microorganisms in a resting or dormant phase may escape destruction. These are termed "persisters" since when they again multiply the resultant organisms are no more resistant than ordinary cocci. These persisters affect the amount of penicillin to be given as well as the administration since it may fail at first to cure a staphylococcic infection due to the presence of these "persisters" (1).

It is possible that penicillin interferes with bacterial nutrition. At all events it appears that effective concentrations of penicillin *in vitro,* or in wounds and body cavities, may be bactericidal by bringing about changes in the surface tension of microorganisms or other lytic effects. Otherwise, and especially when penicillin is injected intramuscularly or intravenously, its therapeutic effects appear to be due

primarily to an inhibitory or bacteriostatic activity with the final destruction of the microorganisms by the antibodies or other bactericidal substances of the blood, especially phagocytosis by the cells of the lymphoid-macrophage or so-called reticulo-endothelial system. As in the case of the sulfonamide compounds, tissues either too old or seriously damaged may not be able to play this essential role in the final disposition of infecting microorganisms.

The question of synergism between penicillin and the sulfonamides is still one of controversy. Some investigators report additive effects whereas others do not.

Certain sulfonamide-resistant organisms such as in gonococcal, pneumococcal, streptococcal and staphylococcal infections in man have proven susceptible to penicillin therapy. At any rate it appears that penicillin therapy and sulfonamide therapy are not antagonistic.

One of the greatest advantages of penicillin has been its relatively low toxicity for man. No other chemotherapeutic compound possesses such a high therapeutic index. The reactions in various cases reported have been due largely to impurities. Urticaria and dermatitis, allergy, and fever have been noted in a few instances.

Administration

Fortunately, penicillin may be administered by many different routes because of its solubility and remarkably low toxicity. As in sulfonamide therapy, the objective in treatment is to bring the infection under control as quickly as possible. In severe infections this is best accomplished by intravenous injections alone or by intravenous injections followed by intramuscular injections. Otherwise, intramuscular injections alone are preferred and are more commonly employed. Absorption is delayed longer and is more variable and irregular after subcutaneous injections which also produce more local irritation with pain or discomfort. Topical applications and injections into cavities, either alone or in conjunction with intramuscular injections, have proven effective in the treatment of localized infections. Oral and rectal administrations are not employed at the present time, principally because of the destruction of considerable amounts of the compound by the hydrochloric acid of the stomach or by penicillinase in the intestinal tract (1).

As in sulfonamide and serum therapy, the dosage of penicillin varies according to the type and severity of infection. At the present

time it is not possible to lay down definite rules although the principles are fairly well established. In general terms the number of units to be administered and the frequency of injections in the treatment of systemic infections should be so arranged as to maintain a sufficient amount in the blood to exert a complete inhibition of growth of the infecting microorganism. In general terms this appears to vary from about 0.02 to 0.2 unit per cubic centimeter of serum. For this reason assays of the serum and other body fluids for penicillin are frequently indicated during treatment although the methods employed are not so frequently or so readily applied as in the case of the sulfonamide compounds. Otherwise and when in doubt, dosage must be based upon clinical judgment and experience alone. The same is true in relation to the duration of treatment which is likewise variable according to the severity and nature of the disease under treatment.

There are many methods employed for the administration of penicillin (1). They are briefly summarized as follows:

Oral and enteral administration:

Intravenous injections	1. Intermittent 2. Continuous 3. Continuous with heparin
Bone marrow injections	
Intramuscular injections	1. Intermittent 2. Continuous
Subcutaneous injections	1. Intermittent 2. Continuous
Cavity injections	1. Intraspinal 2. Intracisternal 3. Intraventricular 4. Intrapleural 5. Intra-articular 6. Intraperitoneal 7. Intraocular
Topical applications	1. Solutions 2. Creams 3. Powders

Penicillin aerosols which are suspensions in air or gas in concentrations of 5000 units per cc. have been found effective when inhaled. There is deep penetration into the lungs followed by absorption into the blood. An oxygen-mask nebulizer or Collison inhalation apparatus may be used.

Topical Methods of Administration

Topical applications of penicillin in solution, incorporated in creams, ointments and in powder form have proven of value in the prevention and treatment of localized infections due to penicillin-susceptible microorganisms such as in wounds, burns and scalds, skin grafts, conjunctivitis, suppurative pneumonitis, etc. Relatively small amounts are required but it is necessary constantly to maintain bacteriostatic concentrations at every point where there are infecting microorganisms until cultures have proven sterile. Otherwise relapses are likely to occur and especially if the applications are stopped too soon. Topical applications of penicillin alone, however, are not so effective as when combined with the parenteral administration of the compound and especially in the treatment of severe sloughing and spreading infections with the danger of septicemia. Needless to state, it is necessary to explore and drain deep pockets of pus and remove all foreign material, sequestra and necrotic tissue so that penicillin therapy alone is not a substitute for adequate surgical measures. As a general rule tissue destruction is stopped and pain relieved along with quicker healing. In wounds gram-negative penicillin-insusceptible microorganisms may appear in great numbers during treatment but they do not significantly delay healing (1).

Local applications of sodium penicillin dissolved in sterile isotonic saline solution carrying 250 to 2500 units per cubic centimeter have proven of value in the prevention of infections of wounds and in the treatment of infected wounds. Solutions are usually preferred to the local applications of penicillin in creams or powders for these purposes. The strength of the solution to employ depends upon the nature and severity of the infection. In infections due to beta hemolytic streptococci, *Staphylococcus aureus* and other microorganisms highly susceptible to penicillin, solutions carrying 250 to 1000 units per cubic centimeter ordinarily suffice. Higher concentrations are

desirable in the case of infections due to less susceptible microorganisms.

For topical application, small Dakin tubes are inserted in the compresses and additional amounts of penicillin solution are administered through the tubes every eight hours. It is imperative that the penicillin solution be trapped at the site of the lesion for a minimum period of six to eight hours.

Irrigations should not be employed except in sinus tracts or deep wounds because the prolonged contact of penicillin with the infected tissues is required. Sprays or wet dressings are to be preferred. Solutions of penicillin may be injected once or twice daily through tubes stitched into wounds after closure, or through a needle into abscess cavities after aspiration of the pus.

Solutions of penicillin carrying 200 to 1000 units per cubic centimeter may be also instilled into the conjunctival sacs at frequent intervals in the treatment of conjunctivitis due to gonococci, meningococci, pneumococci or other penicillin-sensitive microorganisms. Penetration is greatly aided by iontophoresis. They may be also injected subconjunctivally after anesthetization of the conjunctiva with local applications of 5 per cent solutions of metycaine or procaine.

Solutions of penicillin may be also instilled intrabronchially in the treatment of suppurative pneumonitis due wholly or partly to infection with penicillin-sensitive microorganisms. For this purpose daily instillations by bronchial lavage or bronchoclysis are indicated because such methods afford a means of not only removing purulent secretions but for the instillation of relatively large amounts of penicillin in solution capable of reaching areas beyond direct applications through the bronchoscope. Solutions may be also injected once or twice daily through tracheotomy tubes.

For the treatment of various skin infections, blepharitis, burns, scalds, surface wounds or wounds of such a nature that solutions cannot be retained, it is often desirable to apply penicillin in a semi-solid base from which it is slowly liberated. The same is true in preparing granulating wounds and burns for skin grafts since they are more likely to take if coccal infections can be eliminated or controlled.

Several effective and economical creams or ointments which can be absorbed by gauze and may be used for packing wounds, can be

prepared, containing 250 to 1000 units of penicillin per gram of base (see formulas pp. 179 to 184). Such creams should be kept in a refrigerator until used. There is little or no loss of potency in 48 hours. At the end of nine or ten days, however, the potency may drop from 250 to about 160 units per gram and from 250 to about 140 units per gram at the end of two weeks.

The cream may be spread on the wound, but as a rule is spread on the gauze to be applied. A thin layer should cover the area in contact with the wound (it has been estimated that 4 to 8 units per sq. cm. is sufficient), and the application should be made daily or every second day. Before the application of a new dressing, the wound should be adequately cleansed. Skin grafting should not be attempted until three consecutive cultures are negative. *B. pyocyaneus* and *B. proteus* are insensitive to penicillin and sulfanilamide, but these microorganisms interfere only by the mechanical effect of the profuse discharge which may float the grafts away. Several satisfactory ointments for ophthalmic use may also be prepared. Another suitable base is Abbott's hydrosorb base. The ointment is easy to prepare and maintains the potency of penicillin for a considerable time. Excellent results have been obtained particularly in impetigo in newborn infants.

Although previously stated that penicillin is not effective when rectally administered, its use has been recently reported in suppository form (8). Rectal administration has the advantages of simplicity, wide selection of adjuvants and the obvious clinical advantages. With varying quantities of sodium penicillin in a simple cocoa butter base these investigators obtained prolonged, effective penicillin blood levels.

The following precautions should be observed when handling penicillin.

Refrigeration must be a watchword when handling penicillin.

Because temperature appears to be so important, solutions should be made only with cold solvents and chilled utensils.

At least 250 units per Gm. or cc. should be used.

500 units per Gm. or cc. does not appear to be any more effective, although the excess may allow for some dilution, as in cases of excessive serous fluid or tear secretions.

It was found that concentrated solutions of penicillin sodium—10,000 or 20,000 units per cc.—may be prepared under aseptic conditions and stored for about 30 days without significant loss in activity, if constantly refrigerated.

Ointments, eye drops, and wet dressings may be prepared from such concentrated solutions, and will retain their activity, if stored in a refrigerator, for 30 days after the original concentrate was prepared.

Proper allowances should be made in dating the preparations, however, as is illustrated in the following example:

> An ointment prepared from a concentrated solution which was ten days old, should not carry a dating of more than twenty days.

Both ointments and solutions have been used satisfactorily in concentrations of 250 units per Gm. or cc. For preparations that are to be used on mucous membranes, or in the presence of considerable fluids, 500 units per Gm. or cc. may be used. The latter concentration is suggested for eye drops and ophthalmic ointments.

Since the introduction of foreign matter and bacteria into penicillin solutions is believed to result in a reduction of the bacteriostatic activity, care should be exercised at all times to avoid such contamination.

In the preparation of all samples, all utensils and materials, including ointment bases and distilled water, should be carefully sterilized and aseptic conditions maintained throughout the work.

A stock solution of penicillin may be prepared by injecting 10 cc. of cold, sterile, distilled water into an original vial of 100,000 units of the drug from a sterile hypodermic syringe. Each cc. of the resulting solution will contain 10,000 units, and after necessary calculations are made, the desired volume of stock solution may be removed from the vial by means of a small, chilled, sterile, hypodermic syringe (7).

Penicillin powder may be applied to wounds which cannot be closed, or it may be applied preparatory to closure. It should be applied by a blower for even distribution. Enough should be applied for the whole surface of the wound to be covered by penicillin (approximately 8 units per sq. cm. is usually sufficient). As a general rule the powder produces too much pain for application to burns and

scalds. Since the calcium salt of penicillin is not hygroscopic, it has proven quite satisfactory and easily handled for topical application although apt to produce more irritation and discomfort than the sodium salt.

A powder may be prepared containing 500 to 5000 units of penicillin per gram of sulfanilamide diluted 5 per cent with light magnesium oxide. When carrying 1000 units and applied as a frosting it yields about 4 units of penicillin per sq. cm. Sulfathiazole may also be used. The required amount of penicillin should be weighed aseptically, added to the weighed amount of sterile sulfonamide and ground with it in a sterile mortar.

Some have used a snuff composed of 94 parts lycopodium, 5 parts menthol and one part penicillin. It aided in the reduction of pyogenic microorganisms, but was ineffectual in controlling the common cold. Sufficient clinical investigation has not been conducted for evaluating this type of therapy although local applications of suspensions or solutions of penicillin are worthy of trial in the treatment of chronic suppurative sinusitis.

Recently a method was described for incorporating penicillin in slowly dissolving pastilles for maintaining effective degrees of antibacterial and antispirochetal activity in the saliva during the day in spite of its being continuously secreted and swallowed. For use they are placed in the buccal sulcus and allowed to dissolve without chewing or sucking. As one disappears it is replaced by another throughout the day in the treatment of fusospirochetal gingivostomatitis (Vincent's angina), acute tonsillitis, streptococcal carriers, fractures of the mandible compound into the mouth, after difficult extractions with considerable trauma, after tonsillectomies, etc.(1).

Lamellæ or small thin wafers of penicillin have been found as therapeutically effective in ophthalmology as instillations of solutions of penicillin. They have been prepared from penicillin and lactose, for the treatment of conjunctivitis, keratitis, etc. These lamellæ have been found to retain antibacterial activity for as long as two months or more at room temperature and can be placed in the conjunctival sacs at frequent intervals where they slowly dissolve without undue discomfort. Lamellæ prepared with a gelatin base were found unstable and unsatisfactory.

Since the discovery of penicillin, investigators have attempted to find a satisfactory method for oral administration. Sodium citrate has been found to be fairly effective. One gram of anhydrous sodium citrate is administered with a tablet containing 10,000 units of penicillin. The usual dosage would be 3 tablets dissolved in one-half glass of water every 4 hours, one-half hour before meals and 2 doses during the night.

Other methods have been used such as administering penicillin dispersed in various oils, and in water, preceded by magnesium trisilicate to neutralize gastric acidity. The ideal vehicle is still to be found.

Army investigators (20) found that prolonged and effective concentration of penicillin in the blood occurs when oral administration by the method which follows is utilized:

An ordinary gelatin capsule is packed with 100,000 units of penicillin powder in a room kept at 10° F. By filling the capsule at this temperature, the hygroscopic quality of the powder becomes neutralized so that the formation of a gummy mass which rapidly deteriorates is prevented. After the capsule is filled with the powder and sealed tightly, it is taken to room temperature and a transparently thin uniform coating of salol is applied. The enteric capsule thereby produced passes through the stomach unchanged into the small intestine, where absorption occurs. Thus, the well-known destructive effect of the hydrochloric acid in the gastric juice is eliminated.

Single doses (that is, one capsule containing 100,000 units) were given to patients, from whom food and water were withheld for the purpose of establishing constant experimental conditions. Blood was drawn first at fifteen-minute then at half-hour intervals, and penicillin concentrations were determined. The blood levels of penicillin were measured in Oxford units per cubic centimeter. With the employment of this method, 75 per cent of the cases were positive. Concentration of pencillin in the blood rose to levels up to 0.75 unit within the first one-half hour after administration, maintained itself at concentrations of 0.25 unit per cubic centimeter two hours later, and was present even at the end of the third hour at blood values up to 0.09 unit per cubic centimeter.

In all the patients so treated there were no ill effects. There were no signs of intestinal irritation, and the urines obtained showed the usual penicillin excretion but were otherwise negative.

They concluded that previous failures to obtain suitable blood levels via the oral route of administration are probably due to the use of insufficient dosage, ineffective solutions, and improperly prepared capsules.

Experimentation improving the technic of capsule preparation, determining blood levels possible with repeated capsule administration and resultant clinical effects, is now in progress.

Other Microbiotics

A large number of other antibiotic agents have been discovered, but of these only tyrothricin, gramicidin S, streptothricin, patulin, streptomycin and chlorophyll have been employed clinically. All of these with the exception of chlorophyll and streptomycin are too toxic for parenteral administration.

From cultures of *Bacillus brevis* is derived tyrothricin, which is a combination of tyrocidine and gramicidin. Gramicidin and tyrocidine are polypeptids; both contain nitrogen and give positive color reactions for amino acids. Their antibacterial activities *in vitro* are similar to those of surface active compounds of the general class of detergents. Both have been obtained in a crystalline state. Both are soluble in alcohol but insoluble in water and the body fluids. Consequently the basic substance tyrothricin is dispensed commercially in alcoholic solutions requiring dilutions with water (not saline solution) for topical application in the treatment of localized bacterial infections (1).

Gramicidin is twenty-five to fifty times more active against gram-positive microorganisms *in vitro* than tyrocidine. It is particularly active against streptococci (especially beta hemolytic streptococci), various types of pneumococci, most strains of staphylococci, diphtheria bacilli and anaerobic bacilli, but is inactive against the tubercle bacillus. Since it does not destroy the respiration of bacteria, its antibacterial properties appear to depend upon the inhibition of enzymatic activity, retardation of growth and lysis of bacterial cells.

Tyrocidine possesses some activity *in vitro* against such gram-negative microorganisms as *N. catarrhalis, N. intracellularis* (meningococcus), *N. gonorrhœa* (gonococcus); *H. influenzæ* and other gram-negative bacilli. It possesses greater penetrating powers than gramicidin because of a lowering of surface tension and contributes to the solubility and stability of the latter.

Since tyrothricin is a mixture of two active substances, it possesses activity against many different gram-positive and gram-negative microorganisms *in vitro*. Unfortunately, due to its high toxicity it cannot be administered parenterally.

Tyrothricin is supplied by the Mulford Biological Laboratories of Sharp & Dohme for topical application as a concentrate in alcoholic solution requiring dilution with sterile, distilled water which gives a cloudy preparation of the compound in colloidal suspension since it is not soluble in water. Saline solution should not be used since it produces a precipitation of the compound and prevents its even distribution in the diluting medium. The usual concentration for clinical use is 500 micrograms (0.5 mg.) per cc. which is isotonic. For veterinary use they also supply an oil emulsion form.

Tyrothricin is supplied by Parke, Davis & Company as a 2 per cent alcoholic solution and is likewise diluted with sterile, distilled water for topical application. The usual concentrations for topical applications vary from 10 to 50 mg. per cent (0.1 to 0.5 mg. per cc.). Higher concentrations are sometimes employed, but may produce local irritation with pain or discomfort, hyperemia and edema.

If not used within twenty-four hours, suspensions should be discarded and fresh suspensions prepared.

Topical applications of tyrothricin have proven of value in surgical procedures. Local instillations, irrigations and wet packs have been employed in wounds, burns, osteomyelitis, chronic ulcers, sinusitis, mastoiditis, otitis media, streptococcal and pneumococcal empyemas, cystitis, ophthalmic infections, eczematoid dermatitis, furuncles, carbuncles and gonorrhea.

Tyrothricin and also penicillin have potential applications in dental diseases and oral surgery. Many of the microorganisms occurring in the mouth are susceptible to penicillin and still others to tyrothricin. It may be possible in dentistry to use some of the creams with 250 to 1000 units of penicillin per gram in the treatment of pyorrheal pockets and of infected and dry sockets. The dry powder is too irritant for wounds, but it may not be when placed in root canals. The pastilles mentioned previously are of value also (1).

Tyrothricin in a weaker suspension than that usually employed clinically might be necessary in gingivitis to avoid discomfort or pain due to local irritation.

Gramicidin-S

Recent reports from Soviet investigators have announced the development of gramicidin-S. This too is obtained from an aerobic sporulating bacillus of the *B. brevis* type, isolated from garden soil (9).

This substance differs chemically from the gramicidin in tyrothricin. It is also stable and is not destroyed by autoclaving. The name is derived from "Gramicidin Soviet."

Gramicidin-S has specific bactericidal and bacteriostatic effect on staphylococci, streptococci, pneumomocci and some other gram-positive bacteria, and against a number of gram-negative bacteria including *E. coli* and *Proteus vulgaris*. It has also been found effective against the gas bacillus, *Cl. welchii* and *Cl. histolyticum*. Favorable results have been obtained in suppurations of soft tissues, in skin grafting, osteomyelitis, empyema, peritonitis and skin infections. One of the characteristics of its use has been alleviation of pain upon local application.

Pure crystalline gramicidin-S kills staphylococci in a concentration of 3 micrograms and *E. coli* in 50 micrograms per cc. of media. Its toxicity is equal to tyrothricin, although no toxic effects were noted from its external use or from the introduction of it into the pleural or peritoneal cavities in aqueous solution.

Gramicidin-S is employed as 400 mg. of the drug per cc. in water or 70 per cent alcohol. An ointment of a 4 per cent alcoholic solution, diluted fifty times with castor oil, was employed. Best results were obtained in most cases with dilute alcoholic solutions (the original 4 per cent alcoholic solution diluted with water to make 400 to 800 micrograms of gramicidin-S per cc.). In skin infections the stock alcoholic solution is diluted 100 times with 70 per cent alcohol. No conclusions as to its prophylactic value have been presented, although it has been successfully employed in this manner.

Streptothricin is another antibiotic produced in cultures of *Actinomyces lavendulæ*.

Streptothricin is highly active against gram-negative bacilli *in vitro* and especially *Esch. coli, Eber. typhosa, Bact. flexneri, S. schottmülleri* and *Aerobacter aerogenes*. It is also active against gonococci, meningococci and some strains of beta hemolytic strepto-

cocci, but *Staphylococcus aureus,* pneumococci, *Streptococcus viridans, Streptococcus lactis, Proteus vulgaris* and *Ps. pyocyanea* are more resistant. It is also active against numerous molds and yeasts *in vitro.* The smallest amount of streptothricin in 1 cc. of nutrient broth inhibiting the growth of a selected strain of *Esch. coli* has been designated as the unit. Its bacteriostatic and bactericidal activities *in vitro* are stated not to be influenced by blood, serum, peptone or B complex vitamins.

Due to its toxicity, it cannot be administered subcutaneously or intravenously. Solutions containing only 1 mg. per cc. may be of value in treating infected wounds, burns and other local infections.

Patulin

Patulin is produced in cultures of *Penicillium patulum* Bainier, and it is identical with claviformin from *Penicillium claviforme.* This antibiotic has been reported of value in the common cold, but this is still a subject of controversy.

Chlorophyll is also considered with this group. It seems to owe its therapeutic activity to the creation of an unfavorable environment for bacterial growth. It stimulates tissue repair in the promotion of wound healing in solutions of 0.05 to 0.5 per cent. Solutions in saline of 0.2 to 0.5 per cent of chlorophyll with small amounts of propylparahydroxy-benzoate as a preservative, buffered to about pH 6.7, have been proposed for therapeutic purposes by topical application in the form of instillations, irrigations and wet dressings; also ointments containing 1 per cent of water soluble chlorophyll.

Also suggested have been 0.2 per cent solutions of chlorophyll containing 250 units of penicillin per cc.

Topical applications of chlorophyll are stated to be of value in the treatment of infected wounds, indolent ulcers and bed sores, compound fractures, burns, amputation stumps, osteomyelitis, sinus tracts, etc.; also for the treatment of empyema by intrapleural injection, sinusitis, mastoidectomy wounds, purulent conjunctivitis and corneal ulcers, fuso-spirochetal and other types of gingivostomatitis, dry sockets after the extraction of teeth, in preparation for skin grafting, etc., but the exact therapeutic status of the compound cannot be stated at the present time. It has also been used in doses of 500 cc. by intravenous injection at daily intervals for eight days in succession

in the treatment of subacute bacterial endocarditis, but only temporary bacteriostatic effects have been observed (1).

Streptomycin

Streptothricin is being replaced by a new agent, streptomycin, obtained from *Actinomyces griseus.* Its toxicity, apparently due to a histamine-like substance, is not sufficiently high to prohibit its parenteral use (10).

Among the early experimental results were reports that this agent showed *in vitro* and *in vivo* specificity against Gram-positive organisms such as *B. mycoides* and against Gram negatives such as *Ps. fluorescens, Ps. aeruginosa, Proteus vulgaris* and *Serratia marcescens.*

The *unit* of *streptomycin* was established as the quantity of the antibacterial agent which inhibits the growth of a given strain of *E. coli* in 1 cc. of broth or agar, by cup, serial dilution or turbidimetric methods.

Recently published reports of preliminary experiments, however, point to a far more important role in therapy for streptomycin, one which may overshadow its companions streptothricin and tyrothricin, and equal if not excel penicillin in some respects.

These early reports indicated that streptomycin was capable of marked bacteriostatic and bactericidal effect against the human strain of *Mycobacterium tuberculosis,* both *in vitro* and *in vivo.* Because the drug shows a low toxicity for animals, there may open for it a wide field of therapeutic usefulness. Possibly this may rate it as superior to those chemotherapeutic agents which have also been suggested for tuberculosis (diasone, promizole and others of the sulfone series) but whose excessive toxicity prevent their free application in therapy.

Other tests have shown possible usefulness in the treatment of infections caused by *Kleb. pneumoniæ* in man like sinusitis, pneumonia, bronchitis, bronchiectasis, meningitis, etc. It is also likely that streptomycin by intravenous or intramuscular injection will be found safe and therapeutically effective in the treatment of typhoid fever and *B. coli* infections of man in which penicillin and the sulfonamide compounds are apparently ineffective.

Penicillin Formulas

Creams or Ointments:

1. Lanette wax SX*..... 12 parts
   Arachis oil ..... 25 parts
   Distilled water ..... 55 parts
   Penicillin.....250-1000 units per Gm.

2. Lanette wax SX* .....
   Soft petrolatum .....
   Distilled water .....āā equal parts
   Penicillin.....200-400 units per Gm.

Autoclave ingredients together and shake during later stages of cooling to produce an homogenous cream. Then add a concentrated solution of penicillin in sterile distilled water (1).

3. Lanette wax SX*..... 30%
   Distilled water 70%
   Penicillin, q. s. to prescribed unitage

The water and wax are heated to 40° C. and the water slowly mixed into the wax in a mortar, stirring continuously until the mixture is almost cold (usually about ten minutes). The cream is then autoclaved at 20 pounds pressure for 20 minutes. When it has cooled to about 40° C., the correct amount of penicillin, dissolved in a few cc. of sterile distilled water, is added and thoroughly mixed (1).

4. Lanette wax SX*..... 12 parts
   Peanut oil ..... 25 parts
   Distilled water, q. s.....100 parts
   Penicillin sodium, q. s. to prescribed unitage

Melt the wax with the oil on a water bath (60-70° C.) with stirring, and add to it the distilled water heated to the same temperature. Cool to 37° C., rapidly stir in the penicillin sodium solution and *quickly* cool (11).

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* Lanette wax SX is a British preparation. A similar product may be obtained from the R. F. Revson Co., 144 W. 18th Street, New York 11, N. Y. A comparable product may be made of the following: (12) Cetyl alcohol, 90 parts; Sodium lauryl sulfate, 10 parts.

5. Lanette wax SX*..... 10 parts
Castor oil ..... 25 parts
Distilled water, q. s.....100 parts
Penicillin, q. s. to 200 units per gram.

It is suggested that this formula be compounded in the same manner as Numbers 2 and 4 (11).

6. Penicillin..... 100,000 units
Water soluble base ..... 400 Gm.

Sterilize the base in a hot air oven at about 160° C. for half an hour and cool. Mix into it the penicillin. This cream contains 250 units per gram (1).

7. Penicillin..... 100,000 units
Abbott's Hydrosorb ..... 200 Gm.

Autoclave the hydrosorb at 15 pounds pressure for 8 minutes which process liquefies it. When cooled almost to room temperature and still liquid, a solution of 100,000 units of penicillin in 2 cc. of sterile water is rapidly stirred into it. This provides a potency of 500 units per gram (13).

8. Penicillin Sodium ..... 250 units/Gm.
Hydrosorb (sterilized) .....
Aqua Dest. Sterilisata, āā q. s. ad.... 60.0 (7)

The most widely used formula in Canada (21) today is that which is recommended by the R. C. A. M. C. for use in military hospitals. The formula is as follows:

Stearic Acid ..... 20.0 Gm.
**Span No. 60 ..... 10.4 Gm.
**Span No. 80 ..... 2.0 Gm.
**Tween No. 20 ..... 5.6 Gm.
Distilled Water ..... 138.0 Gm.

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* See footnote page 179.

** The Spans and Tween are manufactured by the Atlas Powder Co. They are emulsifiers and wetting agents. Span No. 60 is Sorbitan Monostearate, Span No. 80 is Sorbitan Monooleate, and Tween 20 is a polyoxyalkylene derivative of Sorbitan Monolaurate.

To the distilled water add the other ingredients and autoclave at 17 pounds pressure for 20 to 30 minutes. When nearly cool, stir thoroughly to obtain a smooth cream base. Keep the base refrigerated and sterile. Prepare aseptically a solution of sodium penicillin of such strength that each cc. contains 10,000 units. To the above quantity of base add

Penicillin solution (as described)	4 cc.
Sterile 5% solution disodium hydrogen phosphate	10 cc.
Sterile 5% solution potassium dihydrogen phosphate	10 cc.

Mix these solutions thoroughly into the cream using aseptic technic, to obtain a cream containing 200 units of penicillin per gram. This cream is said to be stable at refrigeration temperature (below 10° C.) for 1 month, at room temperature for 1 week, and at body temperature for 4 days. The phosphates used are a buffer combination which assure a pH of 6.5, the optimum for penicillin stability.

Ophthalmic Preparations—

Ointments:

1. Penicillin	500 units
Petrolatum or hydrous wool fat	25 parts
Cold cream	75 parts (1)
2. Penicillin Sodium	500 units/Gm.
Hydrosorb (sterilized)	
Aqua Dest. Sterilisata āā q. s. ad	4.0 Gms. (7)
3. Penicillin	100,000 units
Mineral oil	10 %
Lanolin, anhydrous	25 %
White petrolatum, q. s.	100 %

Levigate the penicillin sodium with the mineral oil, and incorporate the mixture with the anhydrous lanolin and the white petrolatum (7).

4. Penicillin	100,000 units
Cholesterin	3 %
Cottonseed oil	3 %
White petrolatum	94 %

Adjust the concentration so that 100 Gm. contains 100,000 units. Incorporate the penicillin in 2 cc. of water (11).

5. Simple ointment. U. S. P.
Penicillin (sodium), q. s. to 2500 units per gram.

Levigate the penicillin sodium with Simple Ointment to a smooth consistency; or if the Simple Ointment is to be compounded, 2 to 3 cc. distilled water solution of penicillin sodium may be rapidly incorporated after the base has been cooled to 37° C. and the ointment then *quickly* cooled (11).

Drops:

1. Penicillin Sodium ..... 250 units/cc.
Isotonic Solution of Sodium Chloride (sterilized),
q. s. ad 8.0 cc. (7)

Wafers for Insertion in the Eye:

1. Penicillin .....
Lactose .....āā sufficient quantity (1)

Powders:

1. Penicillin ..... 500-5000 units
Triturate of sulfanilamide or sulfathiazole 5% with light magnesium oxide ..... 1 Gm. (14)
2. Penicillin ..... 3000-4000 units (15)
Dried human serum ..... 1 Gm.
3. Penicillin ..... 10,000-20,000 units
Dehydrated plasma ..... 0.2 Gm. (16)

Snuff:

1. Penicillin ..... 1 part
Lycopodium ..... 94 parts
Menthol ..... 5 parts (1)

Pastilles:

1. Gelatin powder ..... 440 gr.
Methyl parahydroxybenzoate .... 2.5 gr.
Simple syrup ..... 2 f ℥
Distilled water ..... 2 f ℥
Penicillin sodium, q. s. ..... 250-500 units
per pastille

(Note: The above formula will make 200 pastilles of a 1 sq. cm. area and a 0.5 cm. thickness.)

Dissolve the methyl parahydroxybenzoate in boiling distilled water, add the simple syrup, stir in the gelatin and when well mixed, pour into a mold lubricated with persic oil. Stir the melted base until the temperature reaches 43° C. and then quickly add the required amount of penicillin sodium dissolved in a minimum of distilled water. Stir with a glass rod to distribute the penicillin sodium evenly, cool, and cut into pastilles (17).

2. Agar ..... 8 Gm.
Distilled water ..... 200 cc.

Autoclave the agar and water for 30 minutes, and then filter through non-absorbent cotton while still hot. The filtered agar is placed in a water bath at 50 to 55° C. When the agar has cooled to about 50° C., the desired quantity of penicillin solution is added and the mixture is made into pastilles 5 mm. thick.

A simple method for making the pastilles is to pour the molten mixture into a perpendicular length of 16 mm. glass tubing, the lower end of which has been closed with a rubber stopper. After the agar has set firmly (three to four hours), the stopper is removed, and the column of agar can be readily extruded by elevation of one end, and then cut in slices 0.5 cm. thick (18).

If the pastilles are to be stored for several weeks, butyl parahydroxybenzoate may be added to prevent mold growth.

Oil Suspension:

1. Bleached Beeswax, U. S. P. 6%
Peanut oil 94%

(1) Melt U. S. P. bleached beeswax with heat and filter through six layers of gauze; (2) filter peanut oil through Seitz filter; (3) sterilize the pipets, syringes, needles, beeswax, and peanut oil by autoclaving at 17 pounds pressure for twenty minutes; (4) for use heat the sterile beeswax until clear and liquid and with a warm sterile pipet add sufficient to the sterile peanut oil heated to 37° C. to give the desired concentration of 0.75, 1.0, 2.0, 3.0, 4.0, 5.0 or 6.0 per cent and shake thoroughly at room temperature; (5) thoroughly shake an

ampul of calcium penicillin by hand and transfer the contents to a warm (37° to 40° C.) dry, sterile bottle or vial and add 2 to 3 cc. of the clear, warmed beeswax-peanut oil mixture with a warm sterile pipet; (6) add three to five sterile glass beads, stopper with a sterile rubber stopper and shake by hand for ten to fifteen minutes until the particles of penicillin are well dispersed. The beeswax and the peanut oil may also be sterilized in a hot air sterilizer for an hour at about 170° C. (1).

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SELECTED ABSTRACTS

Use of Aluminum Hydroxide and Other Nonabsorbable Antacids in Treatment of Peptic Ulcer. E. N. Collins. *J. A. M. A. 127,* 899 (1945). Favorable results were obtained in the treatment of more than 3,000 cases of peptic ulcer by a system of treatment including the administration of aluminum hydroxide or phosphate gel.

The medical management of these cases included special attention to diet and to interval feedings between meals. Aluminum hydroxide gel was administered by one of two methods which are described. After three months of such treatment, a third method is recommended for the balance of the first year and at such times during at least five years as the patient may experience seasonal recurrences, upper respiratory infections or emotional disturbances.

The author has found the liquid preparations of alumina gel or magnesium trisilicate, or combinations of the two, to be more effective antacids than powder, tablet or capsule preparations. He employs aluminum phosphate gel for two to three months after any surgical procedure for peptic ulcer, particularly for recurrent jejunal ulcer, and also for cases in which there is also diarrhea or evidence of pancreatic deficiency.

The alumina gels possess a prolonged antacid effect and the power to inactivate pepsin. In addition, their astringent and demulcent properties are valuable, and they do not cause a compensatory stimulation of acid secretion, as sodium bicarbonate does. In none of the cases treated was there a disturbance of the acid-base balance or the development of urinary complications.

Antimony Intoxication. T. E. P. Gocher. *Northwest Med. 44,* 92 (1945). Antimony is often used in combination with other metals, chiefly lead, in welding and in stereotype work in printing. Poisoning may occur from inhalation and ingestion of antimony dust. If lead poisoning is also present, the patient responds less readily to treatment. Antimony does not cause the severe nerve reactions that lead

poisoning may produce, and the danger of the development of a permanent disability is much less.

Antimony has an affinity for the large intestine and may thus cause diarrhea, though constipation is occasionally present. In antimony poisoning there may be loss of appetite, nausea, diarrhea, vomiting, headache, dizziness, and irritation of the upper respiratory tract. Perspiration appears to result in the appearance of pustules on the arms, thighs and chest. Irritation of the nose and mouth may be present. The urine may contain albumin or traces of sugar.

In the acute form of antimony poisoning there may be rhinitis, bronchitis, gastric disturbance, colic, faintness, and feeble heart. Symptoms of the chronic form of intoxication may include occipital headaches, dizziness, oppression in the chest, muscular pains, and an eosinophilia to the extent of 20 per cent. Moderate anemia and leukopenia may be observed.

Antimony intoxication and absorption can readily be ascertained by studying the reticulocyte count, which always increases. This was usually found to vary between 30,000 and 60,000 per cu. mm., though in one case a count of 168,000 was noted.

Failure of Mapharsen as an Adjuvant to Atabrine in the Treatment of Relapsing Tertian Malaria. C. F. Kay. *J. A. M. A. 127,* 984 (1945). Intravenous arsenical therapy has been used for years in India and elsewhere for relief of the clinical symptoms of tertian malaria, although it is known that the benefit is only temporary, an observation which was confirmed by the treatment of a small group of military personnel with mapharsen or neoarsphenamine.

Additional observations were made on a group of 176 patients, in all of whom *Plasmodium vivax* was demonstrated. Of this group, 109 cases were treated with atabrine alone, each patient receiving a total dosage of 2.8 gm. in a period of eight days. Each of the remaining 67 cases received, in addition to the atabrine therapy, the intravenous administration of 0.160 gm. of mapharsen in three divided doses.

All patients were observed for at least 65 days from the time of admission, and some for 140 days. Clinical malaria relapses, with diagnoses confirmed by positive smears, occurred in 74.3 per cent of

the atabrine group and in 71.6 per cent of the atabrine-mapharsen group. Relapses before the fortieth day occurred only in the atabrine group, for which the mean time of relapse interval was 51 days, not differing significantly from that noted for the atabrine-mapharsen group, *viz.*, 57 days.

It is concluded that mapharsen in the dosage administered is of no value as an adjuvant to atabrine in the treatment of relapsing tertian malaria.

Nitrous Oxide Pentothal Anesthesia. C. P. Wangeman. *Northwest Med. 44,* 73 (1945). Nitrous oxide with adequate oxygen and the usual premedication is a useful anesthetic for certain surgical procedures but for others it is inadequate. The intravenous administration of pentothal produces a rapid loss of consciousness; postoperative nausea and emesis are not frequent. It has certain disadvantages based upon its depressant effect on respiration; since the drug is cumulative in its action, subsequent doses increase the depth of depression produced. It contricts the bronchioles and does not obtund laryngeal reflexes. It has been reported by authorities of the U. S. Army Medical Department that a survey of data on anesthetic agents used overseas revealed that the death rate attributable to pentothal was six times higher than from all other agents combined.

The combined use of nitrous oxide and pentothal has been suggested by a number of authors, a technic which Wangeman also recommends. Premedication with morphine sulfate (usually ⅛ gr.) and atropine sulfate (1/150 gr.) is desirable; the sedative effect of the former is useful, and it may lessen the quantity of pentothal necessary. Atropine modifies by dilatation the bronchial constriction produced by pentothal, aids in controlling laryngospasm, and its drying effect on the mucous membranes is desirable. This medication is administered one and one-half hours before anesthesia; if necessary, a second intravenous dose of atropine sulfate is given fifteen minutes before pentothal is injected.

Pentothal sodium in 2.5 per cent aqueous solution is given by a slow, intermittent intravenous injection. Usually a dose of 200 mg. of the drug produces a loss of consciousness. After the inhalation of nitrous oxide and oxygen has begun, the additional injection of 25 to 50 mg. doses of pentothal sodium serves to maintain the desired depth of anesthesia.

The pain-relieving effects of nitrous oxide are thus coupled with the hypnotic effects of a barbiturate; this in effect modifies and makes less serious the disadvantages of either drug used alone.

Nitrous oxide pentothal anesthesia is not recommended for surgery within the peritoneum, though it can be used to supplement field-block or spinal analgesia for abdominal procedures. Pentothal is not the anesthetic of choice for intubation of the larynx, and it is contraindicated in shock, morphine overdosage, liver damage and infections of the neck.

Anemia Therapy: Review of Various Liver and Stomach Fractions and Iron Salts. E. J. Teeter. *J. A. M. A. 127,* 973 (1945). The beneficial effect of raw liver therapy on patients having addisonian pernicious anemia was first announced by Minot and Murphy in 1926.

In 1927 and 1928 Cohn *et al.* described a method for preparing a liver extract of high potency, and in 1930 Whipple and his colleagues described a liver extract which they termed the secondary anemia fraction.

The various steps in the process are as follows:

(1) Raw liver is ground into water at 85° C. It was found that adjustment of the pH was not essential.

(2) The precipitate which formed was filtered off; the filtrate was found to contain the antianemia principle.

(3) By concentrating the filtrate under vacuum, a product termed Cohn fraction D was obtained. The addition of 70 per cent ethyl alcohol to this fraction produced a precipitate.

(4) The precipitate constituted the secondary anemia factor of Whipple. The filtrate, however, was found to possess antianemia activity.

(5) Concentration of the filtrate under vacuum, followed by the addition of 90 per cent ethyl alcohol, resulted in the formation of another precipitate.

(6) The precipitate, which is the Cohn fraction G, was found to produce a satisfactory increase in reticulocytes and subsequently red blood cells. The filtrate was inactive.

The use of precipitants other than ethyl alcohol produces extracts containing the antianemia principle in varying amounts.

In 1929 Sturgis and Isaacs and also Sharp demonstrated that an extract prepared from desiccated fresh whole hog stomach possessed antianemic activity when administered orally.

Several workers now prepared liver extracts for intravenous use. In 1930 papers by Gansslen, by Cohn *et al.*, and by West and Howe reported such research. Castle and Taylor in 1931, by treating the Cohn fraction G with 95 per cent alcohol, secured a precipitate which was readily soluble in water and which was quite free of substances which produced protein reactions. A single intravenous injection of extract derived from 100 gm. of raw liver was found to produce a maximal reticulocyte response within five days and an increase of 1,000,000 red blood cells within ten days.

Attention was directed toward extracts for intramuscular administration, however, when it was observed that delayed reactions occurred afer intravenous injection. In 1931 Strauss, Taylor and Castle succeeded in preparing a satisfactory intramuscular extract from the Cohn fraction G by placing the latter in distilled water, heating, adding a preservative, adjusting the pH to approximately 7.4, and buffering. The filtrate yielded a product of which 10 cc. represented approximately 50 gm. of fresh liver. Intramuscular extracts now available are so concentrated that doses of 1 cc. or less need not be repeated oftener than ten or fifteen days.

The bulk or volume of oral extracts still remains rather large, though Walden and Clowes found in 1932 the digestion of stomach tissue with liver tissue yielded a product three or four times as potent as the original raw liver. Similar results were obtained by treating the Cohn fraction G with fresh ground stomach tissue.

Since addisonian pernicious anemia is primarily a disease of the gastrointestinal tract, the antianemia factor in oral products may not be absorbed effectively, especially in the acute stages of primary anemia. Intramuscular extracts are preferred because of the small volume per dose and because absorption is assured.

Iron salt therapy. Ferrous salts produce a higher percentage hemoglobin rise than equal doses of ferric salts. A good average daily dosage of ferrous sulfate is 1 gm.; the dose of iron and ammonium citrates should be from two to three times this amount.

The dosage of liver extracts and iron salts cannot be arbitrary; red blood cell counts and hemoglobin determinations are necessary as measures of the efficacy of antianemia therapy.

The Antibacterial Properties of Dicumarol. A. Goth. *Science 101,* 383 (1945). Although dicumarol has been extensively studied, it has not been recognized previously that this compound possesses antibacterial properties. The growth inhibitory effect of dicumarol against fourteen species of bacteria was observed to be as follows:

A 1:100,000 concentration of dicumarol inhibited the growth of *Staphylococcus aureus, Strepococcus pyogenes, S. viridans,* and *Bacillus anthracis,* and at 1:25,000 that of *Corynebacterium diphtheriæ* and *Brucella abortus.*

A 1:25,000 concentration of the drug failed to inhibit the growth of *Streptococcus fecalis, Bacillus subtilis, Clostridium welchii, Eberthella typhosa, Escherichia coli, Salmonella paratyphi* A, *Proteus vulgaris,* and *Pseudomonas pyocyanea.*

New Strains of Penicillium Notatum Induced by Bombardment With Neutrons. W. G. Myers and H. J. Hanson. *Science 101,* 357 (1945). Moderately heavy spore suspensions in normal saline solution of a stable variant isolated from a strain of *Penicillium notatum* were bombarded with neutrons from a 42-inch cyclotron. On the first day, tubes containing the suspensions were removed after 1, 2, 3½, 4½, 5, 6 and 7 hours when the beryllium target was being bombarded by 10 mev deuterons. Other targets were also used in subsequent trials. On succeeding days additional tubes which received longer treatment were removed.

Approximately 100 new strains or mutations have been isolated from cultures of the treated spore suspensions. Preliminary experiments indicated that the antibiotic activity produced by many of the new strains does not differ qualitatively from that of the parent strain in inhibiting the growth of various bacteria.

Further investigation is in progress.

BOOK REVIEWS

The Chemistry and Pharmacy of Vegetable Drugs. By Noel L. Allport. 1944. 258 pages with illustrations. Chemical Publishing Co., Inc., Brooklyn 1, N. Y. Price: $4.75.

This is an American printing of the original which was published in England. It presents certain data with respect to vegetable drugs which although not comprehensive is interesting as collateral reading.

One cannot help but realize that the galenicals considered in this text will continue to wane in importance in the light of modern therapy and this is all the more poignant since our pharmaceutical cousins in England seem in many respects to be somewhat more slow to relinquish the venerable preparations of a few decades past.

The American reader will find in this text little of modern interest but it does have an approach and give one a viewpoint that is interesting and different. The fact that it is based on English official standards and formulæ may be somewhat confusing to some but a useful comparison to others. Its price is possibly somewhat disproportionate to its relatively small size and contents.

A Concise Pharmacology and Therapeutics. By F. G. Hobart, Ph. C. and G. Milton, M. D., M. R. C. P. Second Edition. 168 pages, including index. Leonard Hill, Ltd., 17 Stratford Pl., W. 1, London. 1944. Price: 12s. 6d.

Patterned in some respects after an "Epitome" or our own "Useful Drugs," this is a very condensed version of a pharmacology text. The subject matter is largely devoted to a discussion of the names, properties and uses of a variety of British and American drugs. Very little space is given to experimental pharmacology or to the mechanism of drug action.

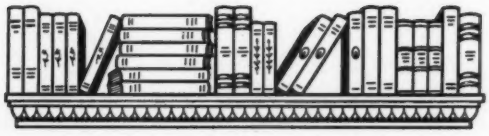
American pharmacists will hardly find this book of sufficient importance to warrant its purchase unless it is for the purpose of making comparisons between drugs used domestically and in England and even in this instance other references are more complete.

Fundamentals of Pharmacology. By Clinton H. Thienes, M. D., Ph. D. Professor of Pharmacology, University of Southern California School of Medicine. xviii+497 pages, including index. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, N. Y. Price: $5.75.

This book was prepared primarily as a text for medical students. The large encyclopedic works like Goodman and Gilman have their place as comprehensive texts and reference books, but Thienes has done an excellent job of eliminating the non-essentials and condensing his subject matter into what a teacher of pharmacology might reasonably expect his students to master.

The book is written with an exceptional clarity of style which is a great help to one who is none too familiar with the subject. It, furthermore, does not overlook the practicalities of pharmacology in that it discusses not only the pharmacodynamics of the various drugs but also the proper method of administering them to patients. This latter point is all too frequently overlooked in many books and yet it is after all the most essential knowledge of all.

Pharmacists and teachers of pharmacology in colleges of pharmacy will find this book worthy of their attention.



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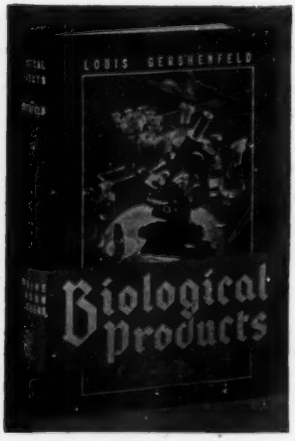

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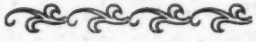

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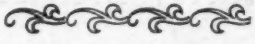

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